REMARKS

Amendments to the Specification

The "RELATED APPLICATION" paragraph of the Specification (page 1, lines 3-7) has been amended to indicate that U.S. Application No. 08/954,279 issued as U.S. Patent No. 6,423,501 on July 23, 2002.

The figure legend for Figure 5 (page 4, lines 17-18) has been amended to recite SEQ ID NOs.

Amendments to the Claims

Claim 8 has been amended to recite "an allergic or inflammatory condition associated with FcεRI-mediated degranulation and/or FcγRIII-mediated degranulation." Support for this recitation can be found, for example, at page 2, lines 18-19, page 14, line 24 to page 15, line 6 and page 17, line 29 to page 18, line 12.

Support for new Claims 42-44 can be found, for example, at page 14, lines 4-7

Support for new Claims 45 and 46 can be found, for example, at page 13, lines 26-29.

Support for new Claim 47 can be found, for example, at page 16, line 23 to page 17, line 6.

Support for new Claim 48 can be found, for example, at page 11, lines 1-10 and page 14, lines 8-23.

The amendments to the Specification and claims, as well as the new claims, are supported by the subject application as originally filed. Therefore, this Amendment adds no new matter.

Substitute Sequence Listing

Filed concurrently herewith is a Transmittal of Substitute Sequence Listing and Preliminary Amendment, a Substitute "Sequence Listing" in paper form (sheet 1/1) comprising SEQ ID NOS:1-3 for the above-identified patent application as required by 37 C.F.R. §§ 1.825(a) and 1.821(c), and a copy of the Substitute "Sequence Listing" in computer readable form as

required by 37 C.F.R. §§ 1.825(b) and 1.821(e). The Substitute "Sequence Listing" is being filed to correct certain informalities. As directed in the Transmittal of Substitute Sequence Listing and Preliminary Amendment, please replace the "Sequence Listing" filed on December 5, 2001 (sheets 1/2 through 2/2) with the attached Substitute "Sequence Listing."

Additional remarks are set forth below with reference to the numbered paragraphs in the Office Action.

Paragraph 3. Compliance with Sequence Rules

In the Office Action, the Examiner states that the application fails to comply with the sequence rules, 37 C.F.R. §§ 1.821-1.825, because Figure 5 contains sequences that have not been identified using SEQ ID NOs. The figure legend for FIG. 5 has been amended to recite SEQ ID NOs. In addition, as described above, a Substitute Sequence Listing is being filed concurrently herewith to correct certain informalities.

Paragraph 4. Objections

The Examiner objects to the specification because the RELATED APPLICATIONS paragraph does not recite that parent application 08/954,279 has issued as U.S. Patent No. 6,423,501. This paragraph has been amended to reflect that U.S. Application No. 08/954,279 issued as U.S. Patent No. 6,423,501 on July 23, 2002.

Paragraph 5. Specification

The Examiner objects to the specification because it is informal in its arrangement. Specifically, the Examiner states that the specification should be arranged beginning with the Title of the Invention, followed by the Cross-References to Related Applications, and should not contain any writing above the title (e.g., Attorney's Docket No., Inventors, Express Mail Label, etc.). Applicants are not aware any rule that prohibits inclusion of such identifying helpful information. If the Examiner maintains this objection, he is respectfully requested to provide reference to the rule requiring deletion of such information.

Paragraph 6. Rejection of Claims 8, 9, 21-26 and 39-41 Under 35 U.S.C. § 112, Second Paragraph

Claims 8, 9, 21-26 and 39-41 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that applicants regard as the invention.

Claim 8

The Examiner states that Claim 8 is indefinite because "it is not clear what is degranulated by 'IgE-mediated degranulation.'" (Office Action, top of page 4). While disagreeing with the Examiner that the phrase 'IgE-mediated degranulation' is indefinite, in an earnest effort to expedite prosecution and allowance of the claimed subject matter, Applicants have amended independent Claim 8 to recite "[a] method of treating an allergic or inflammatory condition associated with FcεRI-mediated degranulation and/or FcγRIII-mediated degranulation." The specification clearly teaches the role that FcεRI and FcγRIII have in degranulation (e.g., of mast cells, of basophils) (see, e.g., specification, page 6, line 1 through page 12, line 16). For example, with respect to the role that FcεRI has in degranulation, the specification teaches:

> Cross-linking of FcεRI-IgE complexes on mast cells and basophils by multivalent antigen initiates a signaling cascade characterized by tyrosine kinase activation, calcium release and influx and, later, by degranulation and release of inflammatory mediators (Jouvin *et al., J. Biol. Chem.,* 269:5918-5925 (1994); Penhallow *et al., J. Biol. Chem.*, 270:23362-23365 (1995); Scharenberg *et al., EMBO J.*, 14:3385-3394 (1995); Lin *et al., Cell,* 85:985-995 (1996); and (Paul *et al., Adv. Immunol.*, 53:1-29 (1993)).

Specification, page 6, lines 5-11, emphasis added.

The specification further teaches:

> Following initial tyrosine kinase activation events, FcεRI signaling, like that of other antigen receptors, involves calcium release from the endoplasmic reticulum (tyrosine kinase-dependent) and a calcium influx, both of which precede degranulation and the release of preformed mediators by granule fusion with the cytoplasmic membrane.

Specification, page 10, lines 25-29, emphasis added.

With respect to the role that FcγRIII has in degranulation, the specification teaches, for example:

> RBL-2H3 cells express FcεRI, CD81 and endogenous rat FcγRIII receptors. However, no high-affinity reagent (antibody) is available to trigger the FcγRIII receptors on RBL-2H3; the 2.4G2 antibody (anti-mouse FcγRII/FcγRIII) was used for this purpose. To demonstrate that CD81 stimulation inhibits degranulation induced through FcγRIII signaling as it does for FcεRI, murine FcγRIIIα chain cDNA was expressed in RBL-2H3 cells.
>
> FcγRIII binding of IgG is detectable only when IgG is present in the form of IgG-containing immune complexes which cross-link FcγRIII receptors and initiate intracellular signals. One of the methods of triggering FcγRIII is through stimulation with crosslinked anti-FcγRIII antibodies. Figure 12 shows the results when RBL-2H3 and FcγRIII-transfectants of RBL-2H3 were loaded with ^{3}H-serotonin in the presence (DNP-HSA stimulation) or absence (immune complex stimulation) of DNP-specific IgE. After overnight incubation, cells were washed and incubated with culture media or media containing 200 ng of anti-rat CD81 mAb 5D1 prior to triggering with optimized concentrations of DNP-HSA or with preformed immune complexes of 2.4G2/anti-rat IgG $F(ab')_2$. Degranulation was allowed to proceed for 30 minutes at 37°C and released ^{3}H-serotonin was quantitated by scintillation counting. As shown in Figure 12, DNP-HSA induces IgE-mediated degranulation in all four cell lines which is inhibitable by anti-CD81 mAb 5D1. 2.4G2/anti-rat IgG F(ab')2 preformed complexes, but not anti-rat IgG F(ab)2 alone, induce degranulation only in cells expressing mFcγRIII receptors (RBL-2H3 transfectants A10, D10 and H11), a process which is also inhibitable by preincubation with 5D1. This data provides the identification of CD81 as a common inhibitor of both FcεRI and FcγRIII.

Specification, page 17, lines 23 to page 18, line 12, emphasis added.

Therefore, in view of the detailed teachings of the specification and the knowledge in the art, the recited phrase "FcεRI-mediated degranulation and/or FcγRIII-mediated degranulation" is not indefinite. Accordingly, reconsideration and withdrawal of this rejection are respectfully requested.

In the Office Action, the Examiner further states that it is unclear "which allergic and inflammatory conditions are associated with IgE-mediated degranulation so as to allow the metes and bounds of the claim to be determined." Office Action, top of page 4. As described, Applicants have amended independent Claim 8 to recite "[a] method of treating an allergic or inflammatory condition associated with FcεRI-mediated degranulation and/or FcγRIII-mediated degranulation." As described above, the specification teaches the role that FcεRI and FcγRIII have in degranulation and release of inflammatory mediators (see, e.g., Specification, page 6, lines 2-11). The specification further teaches that mast cells are important in allergic reactions, anaphylactic reactions and related diseases (see, e.g., Specification, page 13, line 26 *et seq.*). Moreover, the specification teaches particular allergic or inflammatory conditions that can be treated using the methods of the invention (see, e.g., Specification, page 3, lines 1-2, page 13, lines 26-29 and page 19, lines 3-12). Therefore, in view of the detailed teachings of the specification and the knowledge in the art, it is not unclear what allergic or inflammatory condition are associated with FcεRI-mediated degranulation and/or FcγRIII-mediated degranulation. Accordingly, reconsideration and withdrawal of this rejection are respectfully requested.

Claim 23

In the Office Action, the Examiner rejects Claim 23 under 35 U.S.C. § 112, second paragraph, as being indefinite and unclear as to what is meant by contact sensitivity (Office Action, top of page 4). Contact sensitivity is a condition and/or symptom that is known to those of skill in the art. For example, Tanaka *et al.* (*Arch. Dermatol. 130(11)*:1393-1401 (1994); the abstract of which is provided as Reference AY4 in the Supplemental Information Disclosure Statement being filed concurrently herewith) teach that eczematous skin lesions are produced by cell-mediated allergic contact reactions and that contact sensitivity has been demonstrated in patients with atopic dermatitis (Tanaka *et al.*, abstract). In addition, Sussman *et al. (Ann. Intern. Med. 122(1)*:43-46 (1995); Reference AZ4 in the Supplemental Information Disclosure Statement being filed concurrently herewith) teach that contact dermatitis (type IV delayed hypersensitivity reactions to rubber additives) is the most common immunologic manifestation of

latex rubber allergy (Sussman *et al.* abstract). Such references clearly indicate that "contact sensitivity" is an art-recognized term, and is not indefinite as suggested by the Examiner. Accordingly, reconsideration and withdrawal of this rejection are respectfully requested.

Paragraph 7. Rejection of Claims 8, 9, 21-26 and 39-41 Under 35 U.S.C. § 112, First Paragraph

Claims 8, 9, 21-26 and 39-41 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for a method of treating passive cutaneous anaphylaxis associated with FcεRI antigen receptor and/or FcγRIII antigen receptor-mediated degranulation in mast cells comprising administering to a mammal an effective amount of antibody 5D1 that binds to CD81 and inhibits FcεRI antigen receptor and/or FcγRIII antigen receptor-mediated degranulation in mast cells, does not reasonably provide enablement for treatment of other allergic or inflammatory condition associated with IgE-mediated degranulation (Office Action, page 4, lines 15-24). The Examiner asserts that the scope of the claims covers the use of an undefined agent for treating a diverse list of unrelated allergic or inflammatory conditions, which are inferred to be associated with IgE-mediated degranulation, by administering to a mammal an effective amount of an undefined agent that binds to CD81, at an undefined location, and inhibits IgE-mediated degranulation (Office Action, page 5, lines 3-8).

It is well established that "[e]nablement is not precluded by the necessity for some experimentation such as routine screening." In re Wands, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988). "[A] considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." Id. Accordingly, enablement does not require absolute predictability, but that the person of ordinary skill in the art be able to practice the invention without undue experimentation. Id.

Although disagreeing with the Examiner's assertion that the claimed methods are not enabled, in order to expedite prosecution and allowance of the claims, Applicants have amended independent Claim 8 to recite "[a] method of treating an allergic or inflammatory condition associated with FcεRI-mediated degranulation and/or FcγRIII-mediated degranulation comprising administering to a mammal an effective amount of an antibody that binds to CD81

and inhibits FcεRI-mediated degranulation and/or FcγRIII-mediated degranulation." Applicants disclose and exemplify the screening and identification of two distinct monoclonal antibodies, 1A12 and 5D1, which inhibited IgE-mediated mast cell degranulation (Specification, page 11, line 28 to page 12, line 4 and page 22, lines 7-28). As described above, "a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." In re Wands, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988). Given the detailed teachings in the specification of how to screen and identify antibodies that bind to CD81 and inhibit FcεRI-mediated degranulation and/or FcγRIII-mediated degranulation, it would not require undue experimentation for the person of ordinary skill in the art be able to practice the invention. Indeed, such routine screening is analogous to the screening of hybridomas that the Wands court determined was not undue experimentation.

In the Office Action, the Examiner further states that the deposit of anti-CD81 mAb 5D1 is necessary for the enablement of the current invention because the claims require availability of the deposit (Office Action, page 7, lines 15-17). The Examiner asserts that the specification does not disclose how the anti-CD81 mAb can be isolated without undue experimentation. Id. The Examiner further asserts that the specification does not provide a repeatable method for obtaining anti-CD81 mAb 5D1 and that it does not appear to be a readily available material (Office Action, page 7, line 20 to page 8, line 2).

In contrast to the Examiner's assertion, the claimed methods do not require anti-CD81 mAb 5D1 (except for new Claim 43). Instead, independent Claim 8 is drawn to a method of treating an allergic or inflammatory condition associated with FcεRI-mediated degranulation and/or FcγRIII-mediated degranulation comprising administering to a mammal an effective amount of an antibody that binds to CD81 and inhibits FcεRI-mediated degranulation and/or FcγRIII-mediated degranulation" (emphasis added). Thus, although mAb 5D1 is a particular antibody that binds to CD81 and inhibits FcεRI-mediated degranulation and/or FcγRIII-mediated degranulation, it is not required to practice the claimed invention. Other antibodies that bind to CD81 and inhibit FcεRI-mediated degranulation and/or FcγRIII-mediated degranulation can also be used in the claimed methods. Indeed, the specification discloses such an additional antibody

(mAb 1A12) (Specification, page 11, lines 28-33). Moreover, as described above, the specification further describes a method for screening and identifying antibodies (such as mAb 1A12 and mAb 5D1) that bind to CD81 and inhibit FcεRI-mediated degranulation and/or FcγRIII-mediated degranulation (see, e.g., Specification, page 22, lines 8-28). As described above, such routine screening is analogous to the screening of hybridomas that the Wands court determined was not undue experimentation.

However, in order to expedite prosecution and allowance of the claimed methods, Applicants are currently depositing mAb 5D1 and/or mAb 1A12. Upon receiving a deposit receipt, Applicants will perfect the biological deposits in accordance with 37 C.F.R. §§ 1.803-1.809. Therefore, reconsideration and withdrawal of the rejection are respectfully requested.

With respect to the Examiner's assertion that the claimed methods are not enabled because the specification does not enable treatment of allergic or inflammatory conditions other than passive cutaneous anaphylaxis (PCA), Applicants respectfully disagree. As described in the specification and as is known in the art, PCA is an excellent model of IgE-dependent, mast cell activation (Specification, page 16, lines 23-25). Mast cell involvement in a number of allergic and inflammatory conditions is known in the art. For example, Kuby teaches that "IgE antibodies mediate the immediate hypersensitivity reactions that are responsible for the symptoms of hay fever, asthma, hives and anaphylactic shock." Kuby, J. *Immunology, Second Edition* (W.H. Freeman and Co., New York, 1994), p.129; Reference AR5 in the Supplemental Information Disclosure Statement filed concurrently herewith). Kuby further teaches that other type I IgE-mediated hypersensitivity reactions include, e.g., systemic anaphylaxis, and localized anaphylaxis (hay fever, asthma, hives, food allergies, eczema). *See, e.g.*, Kuby, p. 418, Table 18-1. Accordingly, in view of the teachings of the specification and the knowledge in the art, reconsideration and withdrawal of the rejection are respectfully requested.

Paragraph 8. Rejection of Claims 8, 9, 21-26 and 39-41 Under 35 U.S.C. § 112, First Paragraph

Claims 8, 9, 21-26 and 39-41 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was

filed, had possession of the claimed invention (Office Action, page 8, lines 4-8). Specifically, the Examiner asserts that the claims encompass agents of undefined structure and that the only agent disclosed to function in binding to CD81 and inhibiting degranulation of mast cells is an antibody, anti-CD81 mAb 5D1 (Office Action, page 8, lines 12-15). The Examiner further asserts that the instant disclosure of a single antibody does not adequately describe the scope of the use of the claimed genus, which encompasses a substantial variety of subgenera (Office Action, page 9 lines 2-4).

While disagreeing with the Examiner that the claimed method is not adequately described, in an earnest attempt to expedite prosecution and allowance of the claims, independent Claim 8 has been amended to recite "[a] method of treating an allergic or inflammatory condition associated with FcεRI-mediated degranulation and/or FcγRIII-mediated degranulation comprising administering to a mammal an effective amount of an antibody that binds to CD81 and inhibits FcεRI-mediated degranulation and/or FcγRIII-mediated degranulation." As described, in addition to the anti-CD81 antibody, mAb 5D1, the specification discloses a second anti-CD81 antibody, mAb 1A12, which binds to CD81 and inhibits FcεRI-mediated degranulation and/or FcγRIII-mediated degranulation. Given the detailed teachings of the specification and the knowledge in the art, such a disclosure provides adequate written description to support the claimed methods as amended. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

Supplemental Information Disclosure Statement

A Supplemental Information Disclosure Statement (SIDS) is being filed concurrently herewith. Entry of the SIDS is respectfully requested.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

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